REMARKS

This response is provided in response to the Office Action mailed on January 27, 2004, and the references cited therewith. Applicant notes that in response to the restriction requirement dated September 30, 2003, claims 16-27 are withdrawn without prejudice. Claims 1-15 are now pending in this application.

Information Disclosure Statement

Applicant submitted Supplemental Information Disclosure Statements and 1449 Forms on January 20, 2004 and July 28, 2003. Applicant respectfully requests that initialed copies of the 1449 Forms be returned to Applicants' Representatives to indicate that the cited references have been considered by the Examiner.

§103 Rejection of the Claims

Claims 1-15 were rejected under 35 USC § 103(a) as allegedly unpatentable over Steiner (U.S. Patent No. 4,925,673) in combination with Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606). According to the Examiner, while Steiner discloses encapsulation of pharmacological agents in proteinoid microspheres, and Mathiowitz discloses various methods for making proteinoid microspheres, neither of these references teaches cross-linking of proteinoid microspheres with disulfide bridges. However, the Examiner asserts that Margolin teaches use of reversible cross-linkers. Hence, according to the Examiner, claims 1-15 are obvious in view of this combination of references.

The above rejections under 35 USC § 103(a), with respect to the other references cited, are respectfully traversed.

Claim 1 is directed to proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and crosslinked with a crosslinker that can form a pore upon exposure to a reducing agent. Claims 2 and 5 are directed to proteinoid microspheres comprising a mixture of amino acids that are thermally condensed and crosslinked with particular types of identified cross-linkers. Claim 6, 7 and 10 are directed to therapeutic compositions comprising a therapeutic agent encapsulated within the proteinoid microspheres of the invention. Claims 11, 12 and 15 are directed to an article for wound

treatment comprising a therapeutic agent encapsulated within a proteinoid microsphere of the invention.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings to as to arrive at the claimed method. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (M.P.E.P. § 2143). The teaching or suggestion to arrive at the claimed method and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (M.P.E.P. § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Applicant submits that a *prima facie* case of obviousness cannot be established from the combination of cited references because the references do not teach all the claim limitations, there is no reasonable expectation of success that the references could produce the claimed methods and there is no suggestion or motivation to combine the references so as to arrive at the claimed methods.

Failure to Disclose All Elements

Applicant submits that the references fail to disclose or teach all the claimed elements. In particular, the combination of references fails to teach reversible cross-linking groups on proteinoid microspheres that are made of amino acids where drug release can be triggered by the opening of a reversible cross-linking group on the microsphere. Moreover, the combination of references fail teach that such a reversible cross-link can be removed under physiological conditions (i.e., in serum as described in the present application at page 25), without direct intervention by addition of another reagent, such as a an H_2 catalyst or a hydride.

In particular, as indicated by the Examiner, Steiner (U.S. Patent No. 4,925,673) is limited to disclosure of proteinoid microspheres that are not cross-linked. Hence, Steiner does not disclose or teach proteinoid microspheres that are cross-linked with a cross-linker that can form a pore upon exposure to a reducing agent.

Mathiowitz (U.S. Patent No. 5,271,961) is limited to disclosure of methods for making protein microspheres by mixing a solution of proteins (not amino acids) while evaporating the solvent. As also indicated by the Examiner, Mathiowitz discloses that the proteins employed can be cross-linked with cross-linking agents, but the cross-linking agents described are not thio-labile and generally appear to be irreversible. Hence, Mathiowitz does not disclose or teach proteinoid microspheres made of amino acids that are crosslinked with a crosslinker that can form a pore upon exposure to a reducing agent.

Margolin (U.S. Patent No. 6,541,606) discloses methods for stabilizing biologically active macromolecules by crystallizing them from aqueous solutions using evaporation. Margolin provides no mention or teaching of proteinoid microspheres. According to Margolin, the crystals are useful for stabilizing the macromolecules for storage purposes. Margolin mentions that the macromolecules may be cross-linked after crystal formation and discloses that disulfide linkers can be used for this purpose. *See* Margolin at col. 25-26. However, Margolin teaches that hydrogenolysis using an H_2 catalyst or a hydride is needed to cleave such disulfide linkers. *See* Margolin at col. 25, Table 1. Hence, Margolin is limited to a teaching that intervention is needed to cleave the reversible cross-link and provides no recognition that such a reversible cross-link can be removed under physiological conditions (i.e., in serum as described in the present application at page 25). Hence, Margolin does not disclose or teach proteinoid microspheres (formed from amino acids) that are cross-linked with a cross-linker that can form a pore upon exposure to a reducing agent.

Therefore, each of the cited references is defective in that none of them teach proteinoid microspheres made from amino acids that are cross-linked with a cross-linker that can form a pore upon exposure to a reducing agent.

No Reasonable Expectation of Success

One of skill in the art would not have a reasonable expectation of finding the present invention from the combination of Steiner (U.S. Patent No. 4,925,673), Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606), because none of these references teach that disulfide linker can be cleaved in human serum. Hence, one of skill in

the art would not be motivated to try to use disulfide linkers with proteinoid microspheres in order to generate a pore in the microspheres upon exposure to a reducing agent.

Moreover, the process by which proteinoid microspheres are made is distinct from the processes used by Mathiowitz and Margolin. In particular, the proteinoid microspheres made by Steiner are formed by mixing and heating amino acids to temperatures ranging from about 155 °C to about 180 °C (see, Steiner, at col. 4, Example 1a and at col.12, Example 10a). In contrast, Mathiowitz mixes proteins (not amino acids) in a non-solvent while evaporating the solvent (see, Mathiowitz at col. 2, lines 27-29), and Margolin crystallizes macromolecules from aqueous solutions using evaporation (see Margolin at col. 23, lines 12-21). Moreover, Margolin explicitly teaches that cross-linking should be done *after* crystallization (see col. 24, lines 34-35); and Mathiowitz explicitly teaches that cross-linking should be done either *before* or after formation of the microspheres (see col. 6, lines 20-23). Neither reference describes use of a cross-linking *during* formation of the microspheres. Moreover, given that the conditions used for making microspheres from amino acids are so different from those used by Margolin and Mathiowitz (evaporation of solvent), one of skill in the art would have no reasonable expectation that the teachings on cross-linking agents would be successful when making proteinoid microspheres from amino acids.

No Motivation to Combine

Applicant submits that there is no motivation to combine the teachings of Steiner (U.S. Patent No. 4,925,673), Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606). As described above, Steiner is the only reference disclosing proteinoid microspheres made of amino acids. The proteinoid microspheres described by Steiner are not cross-linked. Neither Mathiowitz nor Margolin provide any mention or teaching of proteinoid microspheres, which are made from amino acids (not proteins) by heating a mixture of amino acids (*see, e.g.,* Steiner, Example 1a). As taught by Steiner, proteinoid microspheres are non-toxic and have many useful properties that can be modulated by altering the composition of amino acids in the mixture used to form the proteinoid microspheres. *See,* Steiner at col. 3, lines 5-29. For example, as disclosed by Steiner, the pH at which proteinoid microspheres are soluble can vary depending upon what

types of amino acids are used to form the proteinoid microspheres. *Id.* According to Steiner, one of skill can readily modulate the solubility, gastrointestinal absorption and other desirable properties of proteinoid microspheres simply by changing the types of amino acids employed. *See,* Steiner at col. 3, lines 5 to col. Line 27. Hence, one of skill in the art would not be motivated to utilize the teachings of Mathiowitz and/or Margolin on cross-linking agents with the teachings on proteinoid microspheres provided by Steiner. In view of the teachings by Steiner, such cross-linking agents would be unnecessary.

Similarly, one of skill in the art would not be motivated to combine the teachings of Mathiowitz and Margolin with Steiner, because both Mathiowitz and Margolin are limited to a disclosure of microspheres or crystals formed from the active agent, i.e., the protein or macromolecule of interest. Hence, one of skill in the art would not seek guidance on proteinoid microspheres from Mathiowitz or Margolin, because neither of these references discloses anything about proteinoid microspheres that are made of amino acids and can be used to encapsulate, but do not comprise, an active agent.

Moreover, when Margolin discloses disulfide linkers, Margolin immediately teaches that hydrogenolysis using an H_2 catalyst or a hydride is needed to cleave such disulfide linkers. *See* Margolin at col. 25, Table 1. Margolin provides no recognition or teaching that such disulfide linkers can be cleaved in human serum without intervention or addition of an H_2 catalyst or a hydride. Similarly, while Mathiowitz mentions some cross-linking agents (e.g. glutaraldehyde), Mathiowitz provides no teaching that a linker formed by such a cross-linking agent can be cleaved in human serum. Hence, one of skill in the art would not be motivated to combine the teachings of Steiner, Mathiowitz and Margolin.

Therefore, Applicant submits that the combination of Steiner (U.S. Patent No. 4,925,673), Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606) does not produce the claimed invention. Applicant requests withdrawal of this rejection under 35 USC § 103(a) of claims 1-15.